REMARKS

Applicants respectfully request entry of the present amendments to the claims and consideration of the following remarks.

STATUS OF CLAIMS

Claims 1-3 and 6-15 are pending. Claim 1 is amended. Claims 4 and 5 are canceled. Claim 1 has been amended to incorporate the limitations of claims 4 and 5, therefore the amendment is supported by the original specification. No new matter has been added.

REJECTIONS UNDER § 102(B) AND (E)

Claims 1, 3, 4-7, 12, and 13 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by US 6,432,449 (Goldenberg). Claims 1-3, 5-9, and 12-15 are rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by US 6,875,432 (Liu). These rejections are respectfully traversed.

The present disclosure relates to stable pharmaceutical compositions of a protein, granulocyte-colony stimulating factor (G-CSF). The G-CSF of the present disclosure is expressed heterologously in the bacteria *E. coli*, and thus is produced in a non-glycosylated form. G-CSF, and especially non-glycosylated G-CSF, is known to be a hydrophobic protein, typically unsoluble under biological conditions. The glycosylation process is understood by those possessing ordinary skill in the art to confer stability on the protein and aid in solubilization. Non-glycosylated G-CSF is known to be unstable in *in vitro* preparations, having a tendency to form non-bioactive aggregations, so various additives have been added to prior preparations in order to increase the stability and solubility of the protein, and aid in preventing aggregate formation. These additives may be undesirable for use in pharmaceutical preparations, however, as described in page 3, fifth full paragraph of the specification. The present invention therefore provides a method of producing aqueous pharmaceutical preparations of biologically active, recombinant, non-glycosylated G-CSF having a relatively long shelf life, without the use of any surfactants or other undesirable additives.

Independent claim 1 defines a stable pharmaceutical composition of G-CSF, wherein the composition has a pH value in the range from 4.2 to 4.8 and comprises a therapeutically effective amount of non-glycosylated G-CSF, and an acid, wherein the composition is free of a surfactant, and wherein the composition is aqueous. The Applicants have found that the claimed pharmaceutical composition has a long shelf life, is physiologically well-tolerated, is simple to use, and is possible to be dosed precisely. (See page 3, lines 27-32).

Goldenberg

Goldenberg discloses a sustained release formulation using biodegradable alginate delayed gels or particles and methods thereof. Example 5 was referenced in the Office Action as allegedly being anticipatory. However, the gel formulated in Example 5 falls outside the scope of present claim 1 because it is a **gel** and not an **aqueous** composition. Further, the pH set forth in Goldberg falls outside the scope of the present claims. While the acetate buffer has a pH of 4.5, the resulting gel composition has a pH of 7.5. (See column 15, lines 43-45).

Therefore, claim 1 and dependent claims 3, 6-7, 12, and 13 are not anticipated by Goldenberg. Reconsideration and allowance of claims 1, 3, 6-7, 12 and 13 are hereby respectfully requested.

Liu

Liu discloses a concentrated protein formulation with reduced viscosity. In doing so, Liu discloses a laundry list of components that may be used as the protein. In particular, Liu discloses in column 6 at least 100 components which may be suitable to use as the protein, including G-CSF. Even if one were to select the G-CSF, Liu does not disclose or differentiate between the glycosylated and non-glycosylated forms of G-CSF.

Therefore, claim 1 and dependent claims 2-3, 6-9, and 12-15 are novel in view of Liu. Reconsideration and allowance of claims 1-3, 6-9, and 12-15 are hereby respectfully requested.

REJECTIONS UNDER § 103(A)

Claims 4, 10, and 11 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Liu in view of US 5,284,656 (Platz) and in further view of US 6,776,983 (Sumida). This rejection is respectfully traversed.

Independent claim 1 defines a stable pharmaceutical composition of granulocyte-colony stimulating factor (G-CSF), wherein the composition has a pH value in the range from 4.2 to 4.8 and comprises a therapeutically effective amount of non-glycosylated G-CSF, and an acid, wherein the composition is free of a surfactant, and wherein the composition is aqueous. The Applicants have found that the claimed pharmaceutical composition has a long shelf life, is physiologically well-tolerated, is simple to use, and is possible to be dosed precisely. (See page 3, lines 27-32).

Liu discloses a concentrated protein formulation with reduced viscosity suitable for subcutaneous administration. (See Abstract). As discussed above, Liu discloses a laundry list of components that may be used as the protein. In particular, Liu discloses at least 100 components which may be suitable to use as the protein in column 6. Liu also discloses over the course of columns 6-11 various antibodies that may be included in the definition of "protein." Further, none of the examples in Liu utilize the G-CSF protein. Even if one were to select the G-CSF out of this huge list and without any specific teaching to do so, Liu does not disclose the non-glycosylated G-CSF.

Platz discloses compositions of G-CSF suitable for pulmonary administration, i.e., aerosol administration. Platz teaches away from delivery of G-CSF by injection, and instead disclose "an effective non-invasive" pulmonary administration of G-CSF. (See column 2, lines 60-62). The formulation of components suitable for an aerosol administration (as taught in Platz) is different from those suitable for an injectable or subcutaneous administration (as taught in Liu). For example, see the comparison in Platz in column 8, lines 1-14, where it is stated that certain components, i.e., surfactants, are necessary for subcutaneous injection but not for aerosol administration. Therefore, one of skill in the art reading Liu would not seek the guidance of Platz as the

two references are directed to two entirely different drug delivery formulations. Further, one of ordinary skill in the art reading Liu would be very unlikely to seek the guidance of Platz based on G-CSF being a possible protein, since G-CSF is one listed protein in a laundry list of at least 100 named suitable proteins. The only way to consider combining the two references is upon impermissible hindsight after reading the Applicants application.

Sumida discloses a stable G-CSF formulation comprising a G-CSF and at least one pharmaceutically acceptable surfactant. The formulation is also taught to have a pH in the range of 6-6.8 (see claim 1). Further, the formulation is disclosed as being substantially free from protein as a stabilizer.

Firstly, one of ordinary skill in the art reading Liu would be very unlikely to seek the guidance of Sumida without first having knowledge of the Applicants' application, since G-CSF is one listed protein in a laundry list of at least 100 named suitable proteins. Further, Sumida discloses a formulation that is free of proteins used as stabilizers. Liu, on the other hand discloses Zn-protein complexes as suitable stabilizers. (See column 25, lines 52-58). The only way to consider combining the two references is upon impermissible hindsight after reading the Applicants application.

For the sake of argument, even if one were to combine Liu with Sumida, one would not arrive at the presently claim 1. Liu discloses a formulation having a pH within a range of 4-5.3 or 6.5-12. One reading Liu in combination with Sumida would select the upper pH range that overlaps with Sumida (i.e., 6-6.8) and the resulting combination would fall outside the scope of present claim 1. Further, Liu discloses the use of a surfactant as a possible component. Sumida requires the use of a surfactant in formulations. Therefore, one reading Liu and Sumida together would include a surfactant in a resulting formulation, which would also be outside the scope of present claim 1, which requires the composition to be free of a surfactant.

Therefore, independent claim 1 and its dependent claims 4, 10, and 11 are nonobvious in view of Liu in view of Platz and in further view of Sumida. Reconsideration and allowance of claims 1, 4, 10, and 11 are hereby respectfully requested.

With regard to the nonstatutory obviousness-type double patenting rejection of claims 1-3 and 8-11 over claims 1-10 of copending Application No. 10583157, a proper terminal disclaimer in accordance with 37 CFR 1.321(c) is being filed with this submission, since both applications are commonly owned. Accordingly, reconsideration and allowance of claims 1-3 and 8-11 are hereby respectfully requested.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

FEES

Please charge Deposit Account No. 12-2355 in the amount of $ 1,050.00 for a three-month extension of time for reply. The Applicants do not believe that there are any other fees associated with this filing. However, if the calculations are incorrect, the Commissioner is hereby authorized to charge any deficiencies in fees or credit any overpayment associated with this communication to Deposit Account No. 12-2355. Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 12-2355.

Respectfully submitted,

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